Fractional flow reserve (FFR) is widely used in clinical practice to assess severity of functional coronary artery stenosis; it is the ratio of distal intracoronary pressure (Pd) to aortic pressure (Pa) measured during pharmacologically induced hyperemia. FFR has been shown to be effective at reducing the rate of stent implantation and improving cardiac outcomes compared with angiographic guidance alone, and its use is supported by international guidelines.1,2 Large clinical studies such as Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) used conditions of maximal hyperemia achieved by central-line administration of intravenous adenosine to estimate FFR. However, intravenous adenosine-induced systemic and coronary vascular beds differentially.

Methods and Results—A total of 283 patients (310 coronary stenoses) underwent coronary angiography with FFR using intravenous adenosine 140 mcg/kg per minute via a central femoral vein. Offline analysis was performed to calculate aortic (Pa), distal intracoronary (Pd), and reservoir (Pr) pressure at baseline, peak, and stable hyperemia. Seven different hemodynamic patterns were observed according to Pa and Pd change at peak and stable hyperemia. The average time from baseline to stable hyperemia was 68.2±38.5 seconds, when both ΔPa and ΔPd were decreased (ΔPa, −10.2±10.5 mmHg; ΔPd, −18.2±10.8 mmHg; P<0.001 for both). The fall in Pa closely correlated with the reduction in peripheral Pr (ΔPr, −12.9±15.7 mmHg; P<0.001; r=0.9; P<0.001). ΔPa and ΔPd were closely related under conditions of peak (r=0.75; P<0.001) and stable hyperemia (r=0.83; P<0.001). On average, 56% (10.2 mmHg) of the reduction in Pd was because of fall in Pa. FFR lesion classification changed in 9% using an FFR threshold of ≤0.80 and 5.2% with FFR threshold <0.75 when comparing Pd/Pa at peak and stable hyperemia.

Conclusions—Intravenous adenosine results in variable changes in systemic blood pressure, which can lead to alterations in FFR lesion classification. Attention is required to ensure FFR is measured under conditions of stable hyperemia, although the FFR value at this point may be numerically higher. (Circ Cardiovasc Inter. 2013;6:654-661.)

Key Words: adenosine ■ angiography ■ blood pressure ■ coronary disease ■ fractional flow reserve, myocardial ■ hemodynamics

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From the International Centre for Circulatory Health, National Heart and Lung Institute, NIHR Imperial College Biomedical Research Centre, and Imperial College NHS Trust, London, United Kingdom (J.M.T., S.N., S.S., R.P., J.M., A.D.H., I.S.M., G.W.M., C.S.B., R.A.F., J.E.D.); King’s College London BHF Centre of Research Excellence and the NIHR Biomedical Research Centre at Guy’s and St Thomas’ Hospital NHS Foundation Trust, the Rayne Institute, St Thomas’ Hospital, London, United Kingdom (K.N.A., T.L., M.Z.K., S.R.); and Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Spain (M.E.-P., J.E.).

Correspondence to Justin E. Davies, MBBS, PhD, International Centre for Circulatory Health, Imperial College, 59–61 N Wharf Rd, Paddington, London W2 1LA, United Kingdom. E-mail justin.davies@imperial.ac.uk

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WHAT IS KNOWN

- Fractional flow reserve (FFR) has been shown to be effective at reducing the rate of stent implantation and improving cardiac outcomes compared with angiographic guidance alone.
- Clinical trial data are almost exclusively based on FFR values measured during maximal steady-state hyperemia induced by intravenous adenosine infusion.

WHAT THE STUDY ADDS

- Intravenous adenosine results in variable and unpredictable changes in systemic blood pressure.
- Measuring FFR prior to attainment of maximal steady-state hyperemia can lead to changes in clinical decision making.
- FFR during maximal steady-state hyperemia may be numerically higher than at other times during measurement.
- Using intravenous adenosine, on average it takes ≥60 seconds to achieve stable pressure conditions suitable for measurement of FFR.
- The heterogeneous hyperemic response of adenosine compounds suggests that new agents with vastly different pharmacological profiles (such as regadenoson) will need further evaluation in clinical outcome trials prior to adoption into routine clinical practice.

Analysis of Hemodynamic Data

Data were analyzed using customized software written in Matlab (Mathworks, Inc, Natick, MA). Baseline and stable hyperemia time points were confirmed by visual inspection of each hemodynamic trace, and peak hyperemia was defined as the lowest FFR within 60 seconds of intravenous adenosine infusion and stable hyperemia as when the hyperemic plateau was reached. This analysis yielded mean Pa, Pd, and maximum Pr measurements at baseline, peak, and stable hyperemia after intravenous adenosine infusion.

Pressure Response and FFR Group Analysis

Data were analyzed to determine mean pressure changes for the entire group in response to intravenous adenosine. Mean time from baseline to stable hyperemia was calculated for the entire group. Mean Δ pressure gradient (Pa−Pd) was also compared. Stenoses were categorized according to direction of mean Pa and Pd change at peak and stable hyperemia, with reference to the previous state. Mean ΔPa, ΔPd, and ΔPr from baseline (expressed in both percentage and mmHg) were
compared between the groups. FFR was calculated using pressure measurements at baseline, peak, and stable hyperemia for all stenoses. Changes in lesion classification between peak and stable hyperemia were analyzed using FFR treatment thresholds of both ≤0.80 and <0.75.

Statistical Analysis
Statistical analysis was performed using STATA version 12 (StataCorp LP, College Station, TX). Two-sample t test was used to compare pressure changes at peak and stable hyperemia with those at baseline. The relationship between ΔPa and ΔPd at peak and stable hyperemia was assessed using single-variant regression analysis and F test. To assess clinical characteristics in relation to likelihood of observing a clinical categorization change in FFR between peak and stable hyperemia, first a univariant logistic regression analysis was performed and then variables were put into a multivariant analysis model. Logistic regression analysis was also used to determine the likelihood of observing a clinical categorization change based on pressure response group. For all tests, P<0.05 was considered significant.

Results
Pressure Recordings
Intravenous adenosine caused a significant decrease in both ΔPa 10.2±10.5 mm Hg (−10.0±10.1%) and ΔPd −18.2±10.8 mm Hg (−19.8±10.3%), P<0.001 for both (Figure 2). The average time from baseline to stable hyperemia after administration of intravenous adenosine was 68.2±38.5 seconds. ΔPa and ΔPd were closely related under conditions of peak (r=0.75; P<0.001) and stable (r=0.83; P<0.001; Figure 3) hyperemia.

On average, 56% (10.2 mm Hg) of the reduction in Pd pressure in response to intravenous adenosine was because of a fall in Pa, and the larger the fall in Pd, the larger the contribution from Pa (Figure 3). For example, when Pd fell by 29 mm Hg, the fall in Pa (23 mm Hg) accounted for 80% of the entire fall in Pd. At stable hyperemia, ΔPa ranged from −58.3 mm Hg decreased below baseline to 24.3 mm Hg increased above baseline. In 19.7% (61/310), Pa was decreased >20 mm Hg at stable hyperemia. In contrast, in 14.2% (44/310), Pa was increased above baseline values. The fall in Pa pressure closely followed the reduction in peripheral Pr, with ΔPr at stable hyperemia being −12.4±15.7 mm Hg (−10.4±11.9%), P<0.001. ΔPa and ΔPr were closely related under conditions of peak (r=0.9; P<0.001) and stable (r=0.9; P<0.001; Figure 4) hyperemia.

Seven different hemodynamic patterns were observed when stenoses were grouped according to direction of Pa and Pd changes at peak and stable hyperemia (Figure 2). In 62.9% (17/27), hemodynamic patterns changed between different stenoses, within the same patient.
Mean resting Pd/Pa ratio (baseline) for the entire study group was 0.92. With infusion of intravenous adenosine, FFR fell to a nadir of 0.79 (peak), before rising to 0.83 with continued adenosine infusion to achieve stable hyperemia. Overall, the fall in FFR at peak hyperemia reflected a disproportionate fall in Pd, driven mainly by an initial relatively smaller reduction in Pa, leading to an increased pressure gradient and lower Pd/Pa ratio. At stable hyperemia, when $\Delta P_d$ more reliably reflects changes in coronary microcirculation, reduction in Pd was less pronounced relative to $\Delta P_a$, leading to a decrease in pressure gradient and an increase in the Pd/Pa ratio. A similar pattern was observed in each of the 7 different hemodynamic groups, with FFR being driven mainly by an initial relatively smaller reduction in Pa, leading to an increased pressure gradient and lower Pd/Pa ratio.

**Figure 2.** Changes in aortic pressure (Pa) and distal intracoronary pressure (Pd) at peak and stable hyperemia. Coronary stenoses grouped according to direction of Pa and Pd change at peak and stable hyperemia. This shows 7 different patterns of response. Mean $\Delta P_a$ and $\Delta P_d$ (mmHg) at baseline, peak, and stable hyperemia are shown for each group and for the total study group.

**PPR Measurements**

Mean resting Pd/Pa ratio (baseline) for the entire study group was 0.92. With infusion of intravenous adenosine, FFR fell to a nadir of 0.79 (peak), before rising to 0.83 with continued adenosine infusion to achieve stable hyperemia. Overall, the fall in FFR at peak hyperemia reflected a disproportionate fall in Pd, driven mainly by an initial relatively smaller reduction in Pa, leading to an increased pressure gradient and lower Pd/Pa ratio. At stable hyperemia, when $\Delta P_d$ more reliably reflects changes in coronary microcirculation, reduction in Pd was less pronounced relative to $\Delta P_a$, leading to a decrease in pressure gradient and an increase in the Pd/Pa ratio. A similar pattern was observed in each of the 7 different hemodynamic groups, with FFR being driven mainly by an initial relatively smaller reduction in Pa, leading to an increased pressure gradient and lower Pd/Pa ratio.

**Figure 3.** Relationship between change in distal intracoronary pressure (Pd) and aortic pressure (Pa) at peak and stable hyperemia. After administration of adenosine, both Pa and Pd fall. A significant linear relationship between fall in Pd (y axis) and Pa (x axis) after intravenous adenosine infusion was found between both peak and stable hyperemia. The reduction in Pd is attributable in part to a reduction in Pa and in part to vasodilatation of the coronary microcirculation.
lower at peak than during stable hyperemia. However, the degree of change varied significantly between groups (Figure 5).

Lesion Classification

The proportion of cases where the classification changed between peak FFR and stable FFR was calculated for both FFR \( \leq 0.80 \) and FFR <0.75. Pd/Pa ratio was >0.8 for all stenoses at baseline. Using the FFR \( \leq 0.80 \) cutoff, lesion classification changed in 9% (28/310) of cases between measurements made at peak and during stable FFR (Figure 1). When the FFR cutoff of <0.75 was used, the proportion of patients in whom classification changed between measurements made at peak and during stable FFR was 5.2% (16/310). For 0.3% (1/310), FFR crossed the grey zone and was <0.75 at peak and >0.80 at stable hyperemia. Results of regression analysis comparing clinical characteristics in relation to likelihood of classification change in FFR between peak and stable hyperemia are summarized in Table 2. There was no significant difference between the likelihood of observing a change in FFR classification in any of the 7 different pressure responses.

Discussion

This is the largest study to investigate the effect of intravenous adenosine on the pressure recordings used to calculate FFR and the first to link changes in peripheral resistance and compliance with changes in the coronary perfusion pressure and measurement of FFR at different measurement time points. Our results are consistent with pressure changes observed in other studies, which were focused mainly on changes in coronary arterial pressure.8–11 The fall in Pd pressure after intravenous adenosine is attributable to a combination of a fall in aortic perfusion pressure, in addition to microcirculatory vasodilatation. Using Pr analysis, a close relationship was found between the changes in Pa pressure and changes in large artery compliance and resistance. This study shows how changes in systemic blood pressure (BP) at peak and stable hyperemia may directly alter the FFR value, and how this could lead to differences in lesion classification irrespective of whether either the FFR \( \leq 0.80 \) or <0.75 treatment thresholds are used.
After intravenous adenosine infusion, we observed 7 different patterns of Pa and Pd. The pattern of Pr change, as a measure of peripheral resistance and compliance, mirrored Pa in each of the 7 groups, which suggests that the mechanism underlying the hemodynamic response to intravenous adenosine is largely mediated by changes in large artery compliance and resistance. A brief initial rise in systemic BP was often observed in the first moments after adenosine infusion. This may result in a fractional flow reserve (FFR) value that crosses the FFR 0.80 clinical treatment threshold, and which is lower than the FFR value when calculated at stable hyperemia. Similar fluctuations are seen when using the pressure gradient (Pa−Pd) or pressure ratio (Pd/Pa).

### Hemodynamic Responses to Intravenous Adenosine

Table 2. Logistic Regression Analysis of Clinical Characteristics in Relation to Observed Clinical Categorization Change in FFR Between Peak and Stable Hyperemia

<table>
<thead>
<tr>
<th>FFR Threshold</th>
<th>≤0.80</th>
<th>≤0.75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>0.96–1.04</td>
<td>0.95–1.05</td>
</tr>
<tr>
<td>Sex</td>
<td>0.74</td>
<td>1.68</td>
</tr>
<tr>
<td></td>
<td>0.30–1.84</td>
<td>0.37–7.67</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.99</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>0.95–1.02</td>
<td>0.92–1.03</td>
</tr>
<tr>
<td>% Luminal stenosis</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>0.98–1.03</td>
<td>0.96–1.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.72</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>0.33–1.59</td>
<td>0.27–2.17</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.44</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>0.19–1.00</td>
<td>0.40–5.46</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.07</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>0.47–2.43</td>
<td>0.02–1.00</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.91</td>
<td>1.98</td>
</tr>
<tr>
<td></td>
<td>0.41–2.03</td>
<td>0.68–5.72</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1.01</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>0.22–4.59</td>
<td>0.11–7.24</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.44</td>
<td>1.75</td>
</tr>
<tr>
<td></td>
<td>0.06–3.39</td>
<td>0.37–8.28</td>
</tr>
<tr>
<td>Troponin positive</td>
<td>1.76</td>
<td>1.68</td>
</tr>
<tr>
<td></td>
<td>0.76–4.07</td>
<td>0.56–5.02</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>0.90</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>0.40–2.05</td>
<td>0.35–2.96</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1.23</td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td>0.15–10.23</td>
<td>0.27–19.57</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; CI, confidence interval; FFR, fractional flow reserve; and MI, myocardial infarction.
from the passage of adenosine through the pulmonary circulation, inducing a short reflex peripheral vasoconstriction. After this reflex response, adenosine acts to decrease peripheral resistance with an associated fall in systemic BP.

Pressure, under conditions of stable hyperemia, is considered to be proportional to blood flow. However, our findings suggest that with central intravenous adenosine infusion, there is often an initial reflex rise in flow, seen as a rise in Pa. If FFR is measured prior to achieving stable hyperemia, the initial rise in Pa together with a large reduction in the Pd leads to the potential for overestimation of lesion severity. In contrast, under stable hyperemia, the FFR value is frequently higher, most often reflecting a fall in Pa and a rise in Pd, compared with peak measurements (Figure 5). It has been hypothesized that this increase in Pd in the face of continued falling Pa perfusion pressure reflects an autonomic vasoconstrictor mechanism of the coronary microcirculation. This has been termed paradoxical microcirculatory vasoconstriction. In such cases, the coronary microcirculation behaves like any other vascular bed—by vasoconstricting under conditions of low perfusion pressure to increase distal intracoronary pressure, and preserve flow.

Although adenosine is used to mimic exercise, recent studies have demonstrated that this pharmacological response differs from that during resistive nonpharmacological exercise. During exercise, both peripheral and microcirculatory resistance falls, and perfusion pressure to the coronary and systemic circulation is preserved by an increased cardiac output, most evident through a widening of pulse pressure. However, during adenosine infusion, Pa falls because of the reduction in peripheral resistance.

Over and above these differential responses between pharmacological and exercise vasodilatation, Siebes et al described the influence of pressure on FFR measurements in a theoretical model. These findings suggest that differential responses in pressure may be more widespread and unpredictable than frequently recognized. Our study supports the findings of this theoretical model and demonstrates that across the general resistance with an associated fall in systemic BP.

Potential for overestimation of lesion severity. In contrast, under stable hyperemia, the FFR value is frequently higher, most often reflecting a fall in Pa and a rise in Pd, compared with peak measurements (Figure 5). It has been hypothesized that this increase in Pd in the face of continued falling Pa perfusion pressure reflects an autonomic vasoconstrictor mechanism of the coronary microcirculation. This has been termed paradoxical microcirculatory vasoconstriction. In such cases, the coronary microcirculation behaves like any other vascular bed—by vasoconstricting under conditions of low perfusion pressure to increase distal intracoronary pressure, and preserve flow.

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Over and above these differential responses between pharmacological and exercise vasodilatation, Siebes et al described the influence of pressure on FFR measurements in a theoretical model. These findings suggest that differential responses in pressure may be more widespread and unpredictable than frequently recognized. Our study supports the findings of this theoretical model and demonstrates that across the range of physiological stenoses routinely studied in assessment of intermediate stenoses, Pa, rather than reduction in coronary microcirculatory resistance, is on average responsible for the majority of the fall in Pd. This effect is most evident with larger falls in Pa and least with smaller reduction in Pa. Furthermore, when a reduction in Pa is large, the perceived reduction in Pd/Pa calculation is not due to a worsening of the stenosis, but due to lower Pa and Pd numbers. For example, if the pressure gradient is maintained constant, but Pa and Pd pressure lowered the pressure ratio (Pd/Pa) will get lower. This gives the artificial appearance that the stenosis has increased in physiological significance, but in fact this is not the case, and it is due to simple mathematics of ratio calculations. This suggests that where cardiac output cannot be increased to overcome the vasodilator-mediated reduction in peripheral pressure, FFR may be liable to be influenced by reduced left ventricular functional reserve.

We observed differences in the response of Pa and Pd when measured in different vessels within the same patients, suggesting that the systemic responses to intravenous adenosine are variable not only between individuals, but also between measurements within the same patient. Such differences are regularly observed with other drugs, which are usually expected to behave differentially within and between patients, frequently having different doses and different actions in different vascular beds in the same individual. It is, thus, likely and not at all surprising to see similar intra- and interpatient differential responses with adenosine. These findings may in part help explain the intrapatient variability of FFR classification.

Impact of Changes in Systemic BP on FFR
In this study, we found that changes in systemic BP caused by intravenous adenosine can lead to alterations in FFR lesion classification potentially affecting clinical management decisions. Specifically, we observed in 1 in 11 (9%) cases, a difference in classification when measurements were made at peak and stable hyperemic pressures using the widely acknowledged 0.8 FFR treatment threshold, and observed a difference in 1 in 19 (5.2%) cases using 0.75 FFR treatment threshold. Furthermore, mean peak and stable FFR values for the entire study group similarly crossed below and above the 0.8 FFR threshold. These findings highlight the importance of measuring FFR once stable hyperemic pressures are achieved as was the methodology followed in the FAME and DEFER studies. Otherwise, this could lead to significant alterations in FFR classification. Ideally, measurements should only be made when stable hyperemia is achieved after 260 seconds of stable intravenous adenosine infusion.

Using intravenous adenosine via a central venous line maintains a steady state, stabilizing hemodynamic conditions, and creates the optimal conditions for physiological lesion assessment. However, even when using the methodology used in the large clinical trials from which the outcome data were generated, differences between peak and stable measurement occurs. Although theses difference may seem small whenever classification and therefore treatment strategy is changed between the initial (numerically lower) FFR measurement and that achieved at stable hyperemia, it will mean that unintentionally clinical decision making (to stent or defer therapy) will be made on a basis different from that used in the studies in which clinical outcome data have been generated. Importantly, all of these patients fall within the clinically important intermediate FFR 0.6 to 0.9 zone, and the impact of this difference in clinical decision making on clinical outcomes has not been rigorously assessed.

Study Limitations
This is the first study to our knowledge to demonstrate the impact of systemic hemodynamic change during measurement of FFR, and further studies are required for validation. This was a retrospective analysis of patients undergoing FFR measurements for assessment of intermediate coronary stenoses (mean stenosis severity, 49%; FFR, 0.83). It is, therefore, representative of a typical clinical workload where assessment of intermediate stenoses is in question, and typical clinical practice. Our study focused on hemodynamic changes attributable to intravenous adenosine infusion; however, some clinicians use bolus intracoronary adenosine. Measurement of FFR using intracoronary adenosine has been validated by large clinical outcome studies and may have less impact on systemic BP than intravenous adenosine. It is possible that differences in classification of FFR between intracoronary and intravenous adenosine may be attributable to the findings of
our study. Future studies, which include systematic measurement of both intravenous and intracoronary adenosine administration, would be needed to confirm this.

Conclusions

Intravenous adenosine significantly affects pressures in both systemic and coronary vascular beds. This can lead to significant differences in diagnostic classification when measurements are made between peak and stable FFR. To maximize the likelihood of obtaining the correct FFR classification, measurements should be made under conditions of stable hyperemia, as performed in the landmark FFR outcome studies.

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Disclosures

Dr Davies is a consultant for Volcano Corporation. The other authors report no conflicts.

References


Hemodynamic Response to Intravenous Adenosine and Its Effect on Fractional Flow Reserve Assessment: Results of the Adenosine for the Functional Evaluation of Coronary Stenosis Severity (AFFECS) Study


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